# Overview of Lactofen FQPA Risk Assessment for Tolerance Reassessment

**September 24, 2003**

## *Introduction*

This document summarizes EPA's human health risk findings for the herbicide lactofen, as presented fully in the documents: *Lactofen: Revisions to HED Tolerance Reassessment Risk Assessment,* dated August 12, 2003; *Lactofen, Preliminary Human Health Risk Assessment for Tolerance Reassessment,* dated October 12, 2000; *Lactofen-Report of the Cancer Assessment Review Committee,* dated May 21, 2002; *Lactofen: Report of the Mechanism of Toxicity Review Committee,* dated March 12, 2002*;* and *Drinking Water Exposure Assessment for Lactofen Updated for Prospective Ground Water (PGW) Monitoring Study*, dated January 21, 2003. The purpose of this summary is to assist the reader by identifying the key features and findings of the risk assessments so that he or she may better understand the conclusions reached in the assessments. This summary was developed in response to comments and requests from the public which indicated that the risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Lactofen is a member of the diphenyl ether group of herbicides, which includes sodium acifluorfen (which shares a major environmental degradate, acifluorfen, with lactofen), nitrofen, oxyfluorfen, and fomesafen. The Agency has evidence that the diphenyl ether group of compounds induce similar toxic effects but has not yet determined whether they exhibit a common mechanism of toxicity. The Agency will determine whether a cumulative risk assessment of lactofen and the other diphenyl ethers is appropriate at a later date. For the purposes of tolerance reassessment for lactofen, EPA is assuming no common mechanism. To date, EPA has only identified two classes of chemicals that share a common mechanism of action. A cumulative assessment is being conducted for these classes (i.e., the organophosphates and a subset of the carbamates). However, EPA did consider the contribution of the acifluorfen degradate from use of the herbicide sodium acifluorfen by conducting an aggregate assessment for acifluorfen derived from both lactofen and sodium acifluorfen sources.

Because lactofen is under review for tolerance reassessment only, no occupational or ecological risk assessment was conducted. The purpose of this review is to reassess lactofen tolerances, for which the Agency only considers risk from food, drinking water, and residential exposures, if appropriate. At this time, there are no residential uses of lactofen; therefore, residential exposure and risk is not considered. The FQPA risk assessments for lactofen and other technical support documents are available on the Internet at www.epa.gov/edockets under docket

number OPP-2003-0194 and in the public docket (under the same docket number) for viewing.

## *Use Profile*

**Selective Herbicide:** Lactofen is registered for use on snap beans, soybeans, and cotton (non-food use) for both pre- and post-emergent control of broad leaf weeds. In the past, lactofen was also registered for use on tomatoes in Florida under an emergency exemption (FIFRA Section 18 registration). Lactofen is not registered for residential use. Although not currently registered, the proposed new food uses of lactofen on peanuts and cotton were included in the risk assessment to support establishment of tolerances.

**Formulations:** Lactofen is sold in the United States under the trade names Cobra® and Stellar®. Lactofen is formulated as technical grade (71.7% active ingredient), manufacturing use product (60% active ingredient), and emulsifiable concentrate (23.2 to 26.6% active ingredient).

**Methods of Application:** Aerial and ground application; band treatment, broadcast, directed spray, low volume spray, soil broadcast treatment, and soil incorporation.

**Use Rates:** Lactofen is generally applied at a rate of 1 lb active ingredient (ai) per acre (A) or less per application with a total application of 1 lb ai/A/year.

**Annual Poundage:** Approximately 235,000 pounds of lactofen a.i. are applied annually to nearly 2.2 million acres. Lactofen's largest markets in terms of total pounds of a.i. applied annually are soybeans (85%) and cotton (12%). The remaining use is primarily on fresh beans. Very limited use has been reported on tomatoes in Florida from a FIFRA Section 18 registration which is now expired.

**Percent Crop Treated:** Sites on which lactofen has the highest percent of crop treated include soybeans (3%) and cotton (2%, non-food use).

**Registrant:** Valent USA Corporation

## *Human Toxicity*

- Lactofen has low acute toxicity via the oral, dermal, and inhalation routes of exposure; causes mild skin irritation; and is not a dermal sensitizer. The manufacturing use product (60% active ingredient) is a moderate eye irritant.

- Lactofen is in Acute Toxicity Category IV for acute oral and inhalation toxicity and Category III for acute dermal toxicity.

## *Human Health Risk Assessment*

### *Acute Dietary (Food) Risk*

Acute dietary risk from food is calculated considering what is eaten in one day. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day and no adverse health effects would be expected) does not exceed the Agency's level of concern. The aPAD is the reference dose (RfD) adjusted for the FQPA safety factor.

The acute dietary analysis uses high-end food residue values from field trial studies and percent crop treated information. The dietary risk assessment was based only on residues of lactofen because metabolites are not expected to be present at significant levels. Because no relevant effects following a single exposure of lactofen were identified for the U.S. general population, an acute dietary risk assessment for the entire U.S. population was not conducted. However, an assessment was conducted for the population subgroup of "females 13-50 years old" because developmental effects were noted in a rat developmental toxicity study. The Agency believes these effects are only relevant to women of child bearing age.

The acute dietary exposure analysis for food is a Tier 2 assessment based on the Dietary Exposure Evaluation Model (DEEM™). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity.

- The acute dietary (food) risk estimate is not of concern for any population group. Acute dietary exposure to lactofen comprises less than 0.1% of the aPAD for females 13-50 years old.

- A No Observed Adverse Effect Level (NOAEL) of 50 mg/kg/day was established for females 13-50 years old based on decreased fetal weight and skeletal abnormalities at a Lowest Observed Adverse Effect Level (LOAEL) of 150 mg/kg/day in a rat developmental toxicity study. The skeletal abnormalities are presumed to occur after a single exposure (dose) and, thus, are appropriate for this acute risk assessment.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and intra-species variation (10X).

- A 3X FQPA safety factor was retained for acute dietary exposures for females 13-50 years old based on the following:

- no increased susceptibility from *in utero* and/or postnatal exposure to lactofen in rats,
- adequate data are available to satisfactorily assess food exposure and to provide a screening-level drinking water exposure assessment, and
- uncertainty due to a data gap for a rabbit developmental toxicity study.

- The aPAD for females 13-50 years old is 0.17 mg/kg/day. No aPAD has been established for the general population.

## *Chronic Dietary (Food) Risk*

For the chronic (non-cancer) dietary (food ) risk assessment, the average consumption value for each population subgroup is combined with average residue values in/on commodities to determine average exposure (in mg/kg/day). A risk estimate that is less than 100% of the chronic Population Adjusted Dose (cPAD) (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) does not exceed the Agency's level of concern. The chronic dietary analysis utilized anticipated residue values based on field trial studies, concentration factors from processing studies, and percent crop treated information.

- The chronic dietary (food) risk estimate is not of concern. Dietary exposure to lactofen constitutes less than 0.1% of the cPAD for the U.S. population and all population subgroups.

- The NOAEL used in the chronic dietary assessment is 0.79 mg/kg/day based on kidney lesions and weight changes to the thyroid and adrenal glands at a LOAEL of 3.96 mg/kg/day, and is derived from a chronic oral toxicity study in dogs.

- The uncertainty factor (UF) is 100 to account for inter-species extrapolation (10X) and intra-species variation (10X).

- The FQPA safety factor is 1X for chronic dietary exposures because the data gap for a developmental toxicity study in rabbits has no bearing on chronic exposure.

- The cPAD is 0.008 mg/kg/day for all population subgroups.

## *Cancer Dietary (Food) Risk*

Chronic (cancer) dietary risk is also calculated by using the average consumption values for food and average residue values for those foods over a 70-year lifetime. Because lactofen is now considered to be unlikely to be carcinogenic at low doses, the chronic exposure value is compared with a NOAEL to determine the cancer risk estimate. Cancer risk for lactofen is now expressed as a Margin of Exposure (MOE), and cancer MOEs greater than 100 for lactofen are not of concern.

- The results of the cancer risk assessment for lactofen show that the cancer MOEs from food alone are 300,000 for the general U.S. population, which is not of concern.

- The Agency revised the cancer classification of lactofen based on several toxicity studies showing that lactofen acts via a peroxisome proliferation mechanism of action. These studies were evaluated using criteria established by the International Life Science Institute (ILSI). Details of EPA's review of the mechanism of action and the cancer classification for lactofen may be found in the following documents: *Lactofen: Report of the Mechanism of Toxicity Review Committee*, dated March 12, 2002 and *Lactofen-Report of the Cancer Assessment Review Committee*, dated May 21, 2002.

- Lactofen is now classified under EPA's 1999 Cancer Risk Assessment Guidelines as "*likely to be carcinogenic to humans at high enough doses to cause these biochemical and histopathological effects [peroxisome proliferation] in the livers of rodents but unlikely to be carcinogenic at doses below those causing these changes*." Lactofen is now considered to be a threshold carcinogen.

- The revised cancer risk assessment for lactofen is based on a NOAEL of 0.3 mg/kg/day from a special 7-week rodent study which evaluated peroxisome proliferation in the liver of rats and mice. Effects observed at the study LOAEL of 10 mg/kg/day included increased liver enzyme activity and histopathological findings in mice. The selected NOAEL is considered to be protective of cancer effects because the changes in liver enzymes and histopathology are believed to precede liver tumor formation for a peroxisome proliferation mode of action.

## *Fate and Transport*

- Lactofen is not persistent in the environment and has a high affinity for binding and low solubility. The primary degradate of lactofen is acifluorfen, which is also a degradate of sodium acifluorfen, another herbicide registered for use in agricultural and residential settings.

- Environmental fate data suggest that, while lactofen is not likely to reach water resources in any significant quantities, its degradate acifluorfen is both persistent and mobile in the environment.

- The acifluorfen degradate derived from sodium acifluorfen is expected to be more likely to leach to groundwater than the same degradate derived from lactofen because the two pesticides degrade using different pathways. Sodium acifluorfen degrades rapidly, sometimes instantaneously, to acifluorfen in the environment. Lactofen degrades via two different metabolic pathways. Also, 100 percent of sodium acifluorfen degrades to acifluorfen, whereas, at most, only 58 percent of lactofen is expected to degrade to acifluorfen. The acifluorfen degradate from use of lactofen is not expected to move through the soil matrix as a single pulse as would be expected with use of sodium acifluorfen.

## *Drinking Water Dietary Risk*

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses either screening-level modeling or actual monitoring data, if available, to estimate those risks. Estimated drinking water concentrations (EDWCs) in groundwater and surface water sources of drinking water were determined for lactofen and the acifluorfen degradate derived from both lactofen and sodium acifluorfen uses.

- Because lactofen is not persistent in the environment and has a high affinity for binding (low mobility), it is not expected to leach to groundwater. Moreover, based on a recently conducted prospective groundwater study, which featured highly vulnerable soils, lactofen was not detected.

- To assess risks of lactofen in drinking water, screening-level modeling was used to estimate the concentration of lactofen in groundwater and surface water. Modeling is generally considered to provide high-end estimates of drinking water exposure. The EDWCs of lactofen from model results are summarized in Table 1.

Table 1. Summary of Lactofen Drinking Water Assessment

| Crop Scenario | Surface Water EDWC (ppb) | Ground Water EDWC (ppb) |
|---|---|---|
| Acute | | |
| Cotton | 0.39 | 0.006 |
| Soybean | 0.18 | 0.006 |
| Chronic (Noncancer) | | |
| Cotton | 0.008 | 0.006 |
| Soybean | 0.008 | 0.006 |
| Cancer | | |
| Cotton | 0.005 | 0.006 |
| Soybean | 0.007 | 0.006 |

EDWC, Estimated Drinking Water Concentration

- To determine the EDWCs of the degradate acifluorfen derived from lactofen in surface water sources of drinking water, a Tier II screening-level model was used. However, due to the complexity of the fate properties of acifluorfen and groundwater model limitations, monitoring data were considered to estimate potential acifluorfen contamination of groundwater from lactofen.

- To consider the contribution of the acifluorfen degradate derived from use of the herbicide

sodium acifluorfen, screening-level models were utilized to determine EDWCs in both groundwater and surface water sources of drinking water. The individual and total EDWCs of the acifluorfen degradate from both lactofen and sodium acifluorfen are summarized in Table 2.

Table 2. Summary of Acifluorfen Degradate Drinking Water Assessment

| Crop Scenario | Surface Water EDWC (ppb)[1] | | | Groundwater EDWC (ppb) |
|---|---|---|---|---|
| | Acute | Chronic (Noncancer) | Cancer | |
| Acifluorfen Derived from Sodium Acifluorfen | | | | |
| Soybeans | 7.47 | 1.91 | 1.10 | 3.67 |
| Peanuts | 4.98 | 1.84 | 1.10 | 3.67 |
| Acifluorfen Derived From Lactofen | | | | |
| Cotton | 2.99 | 0.53 | 0.21 | 0.035[2] |
| Soybeans | 2.65 | 0.52 | 0.24 | 0.035[2] |
| Total Acifluorfen from all Sources | | | | |
| Soybeans | 10.12 | 2.43 | 1.34 | 3.71 |

[1] EDWCs were calculated using the Tier II PRZM/EXAMS model, which utilizes the Index Reservoir Model and is adjusted for the Percent Crop Area (PCA) factor.
[2] EDWCs were derived from prospective groundwater monitoring study

## *Residential Risk*

Lactofen is not registered for residential uses; therefore, the Agency did not assess residential risk.

## *Aggregate Risk*

Aggregate risk considers the combined exposure to pesticides through food, drinking water, and, if appropriate, residential uses. Because there are no residential uses of lactofen, there is no residential exposure to consider in the aggregate risk assessment; therefore the aggregate assessment for lactofen includes exposures only from food and drinking water. To determine the maximum contribution from water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food and then calculates a Drinking Water Level of Comparison (DWLOC). The EDWC derived from either monitoring or modeling is then compared with the DWLOC. EDWCs that are above the corresponding DWLOC exceed the Agency's level of concern.

- An aggregate assessment for lactofen was conducted by comparing the surface water and groundwater EDWCs with the corresponding DWLOCs. As indicated in Table 3, the EDWCs for all exposures were less than the corresponding DWLOCs; therefore, the Agency has no concern for the aggregate risk of lactofen.

Table 3. Aggregate Risk of Lactofen

| Exposure | Surface Water EDWC (ppb) | Groundwater EDWC (ppb) | DWLOC (ppb) |
|---|---|---|---|
| Acute | 0.18-0.39 | 0.006 | 5100 |
| Chronic (Noncancer) | 0.008 | 0.006 | 80 |
| Cancer | 0.005-0.007 | 0.006 | 105 |

- The Agency also conducted an aggregate assessment for acifluorfen, derived from the use of the herbicides lactofen and sodium acifluorfen, by comparing the total acifluorfen surface water and groundwater EDWCs with the corresponding DWLOCs. As indicated in Table 4, the EDWCs for all exposures were less than the corresponding DWLOCs; therefore, the Agency has no concern for the aggregate risk of the acifluorfen degradate from both lactofen and sodium acifluorfen.

Table 4. Aggregate Risk of Total Acifluorfen from All Sources

| Exposure | Surface Water EDWC (ppb) | Groundwater EDWC (ppb) | DWLOC (ppb) |
|---|---|---|---|
| Acute | 10.12 | 3.71 | 600 |
| Chronic (Noncancer) | 2.43 | 3.71 | 40 |
| Cancer | 1.34 | 3.71 | 455 |

- The Agency previously had a cancer risk concern for aggregate exposure to the acifluorfen degradate via groundwater. EPA's conclusions about the cancer risk from the acifluorfen degradate in groundwater have changed as a result of new information on both the nature of the cancer effect and the ability of lactofen (and its acifluorfen degradate) to leach to groundwater. The Agency has no concern for the aggregate cancer risk from either lactofen or acifluorfen.

## *Occupational and Ecological Risk*

As stated previously, no occupational or ecological risk assessment was conducted for lactofen. This review is limited to food and drinking water exposures; hence, review of occupational and ecological risks is not necessary for tolerance reassessment.

## Data Needs

The following confirmatory data requirements have been identified for lactofen:

- Prenatal Developmental Toxicity Study in Rabbits (OPPTS Guideline 870.3700, current data gap, two developmental toxicity studies are required for every food use chemical)

- Confined Rotational Crop Study (OPPTS Guideline 860.1850, required because confined rotational crop study in root crops indicated minimal uptake of radioactivity in carrots and radishes planted after lactofen application).

In addition, product chemistry studies are required for the 60 and 76% a.i. formulations, because the composition of these two products has changed significantly as a result of a change in the manufacturing process.